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Gut Microbes Contribute to Recurrent "Yo-Yo" Obesity

New research in mice may in the future help dieters keep the weight off

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Following a successful diet, many people are dismayed to find their weight rebounding – an all-too-common phenomenon termed "recurrent" or "yo-yo" obesity. Worse still, the vast majority of recurrently obese individuals not only rebound to their pre-dieting weight but also gain more weight with each dieting cycle. During each round of dieting11/12/2018

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and-weight-regain, their proportion of body fat increases, and so does the risk of developing the manifestations of metabolic syndrome, including adult-onset diabetes, fatty liver and other obesity-related diseases.

As reported (http://www.nature.com/nature/journal/vaap/ncurrent/full/nature20

796.html) today in *Nature*, researchers at the Weizmann Institute of Science have shown in mice that intestinal microbes – collectively termed the gut microbiome – play an unexpectedly important role in exacerbated post-dieting weight gain, and that this common phenomenon may in the future be prevented or treated by altering the composition or function of the microbiome.

The study was performed by research teams headed by **Dr. Eran Elinav** (*http://www.w eizmann.ac.il/immunology/elinav/*) of the Immunology Department and **Prof. Eran Segal** (*http://www.wisdom.weizmann.ac.il/~eran/*) of the Computer Science and Applied Mathematics Department. The researchers found that after a cycle of gaining and losing weight, all the mice's body systems fully reverted to normal – except the microbiome. For about six months after losing weight, post-obese mice retained an abnormal "obese" microbiome.

"We've shown in obese mice that following successful dieting and weight loss, the microbiome retains a 'memory' of previous obesity," says Elinav. "This persistent microbiome accelerated the regaining of weight when the mice were put back on a high-calorie diet or ate regular food in excessive amounts." Segal elaborates: "By conducting a detailed functional analysis of the microbiome, we've developed potential therapeutic approaches to alleviating its impact on weight regain."

The study was led by Christoph Thaiss, a Ph.D. student in Elinav's lab. Thaiss collaborated with master's student Shlomik Itav of the Elinav lab, Daphna Rothschild, a Ph.D. student of Segal's lab, as well as with other scientists from Weizmann and elsewhere.

In a series of experiments, the scientists demonstrated that the makeup of the "obese" microbiome was a major driver of accelerated post-dieting weight gain. For example, when the researchers depleted the intestinal microbes in mice by giving them broad-spectrum antibiotics, the exaggerated post-diet weight gain was eliminated. In another experiment, when intestinal microbes from mice with a history of obesity were introduced into germ-free mice (which, by definition, carry no microbiome of their own), their weight gain was accelerated upon feeding with a high-calorie diet, compared to germ-free mice that had received an implant of intestinal microbes from mice with no history of weight gain.

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Next, the scientists developed a machine-learning algorithm, based on hundreds of individualized microbiome parameters, which successfully and accurately predicted the rate of weight regain in each mouse, based on the characteristics of its microbiome after weight gain and successful dieting. Furthermore, by combining genomic and metabolic approaches, they then identified two molecules driving the impact of the microbiome on regaining weight. These molecules – belonging to the class of organic chemicals called flavonoids that are obtained through eating certain vegetables – are rapidly degraded by the "post-dieting" microbiome, so that the levels of these molecules in post-dieting mice are significantly lower than those in mice with no history of obesity. The researchers found that under normal circumstances, these two flavonoids in weight cycling prevented this fat-derived energy release, causing the post-dieting mice to accumulate extra fat when they were returned to a high-calorie diet.

Finally, the researchers used these insights to develop new proof-of-concept treatments for recurrent obesity. First, they implanted formerly obese mice with gut microbes from mice that had never been obese. This fecal microbiome transplantation erased the "memory" of obesity in these mice when they were re-exposed to a high-calorie diet, preventing excessive recurrent obesity.

Next, the scientists used an approach that is likely to be more unobjectionable to humans: They supplemented post-dieting mice with flavonoids added to their drinking water. This brought their flavonoid levels, and thus their energy expenditure, back to normal levels. As a result, even on return to a high-calorie diet, the mice did not experience accelerated weight gain. Segal said: "We call this approach 'post-biotic' intervention. In contrast to probiotics, which introduce helpful microbes into the intestines, we are not introducing the microbes themselves but substances affected by the microbiome, which might prove to be more safe and effective."

Recurrent obesity is an epidemic of massive proportions, in every meaning of the word. "Obesity affects nearly half of the world's adult population, and predisposes people to common life-risking complications such as adult-onset diabetes and heart disease," says Elinav. "If the results of our mouse studies are found to be applicable to humans, they may help diagnose and treat recurrent obesity, and this, in turn, may help alleviate the obesity epidemic."

Also taking part in the study were Mariska Meijer, Maayan Levy, Claudia Moresi, Lenka Dohnalova, Sofia Braverman, Shachar Rozin, Dr. Mally Dori-Bachash and Staff Scientist Hagit Shapiro of the Immunology Department, Staff Scientists Drs. Yael Kuperman and Inbal Biton, and Prof. Alon Harmelin of the Veterinary Resources Department, and Dr. Sergey Malitsky and Prof. Asaph Aharoni of the Plant and Environmental Sciences Department – all of the Weizmann Institute of Science, as well as Prof. Arieh Gertler of 11/12/2018

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Dr. Eran Elinav's research is supported by the Leona M. and Harry B. Helmsley Charitable Trust; the Adelis Foundation; the Else Kroener Fresenius Foundation; John L. and Vera Schwartz, Pacific Palisades, CA; the Rising Tide Foundation; Andrew and Cynthia Adelson, Canada; Yael and Rami Ungar, Israel; Donald L. Schwarz, Sherman Oaks, CA; Leesa Steinberg, Canada; Valerie and Aaron Edelheit, Santa Barbara, CA; Jack N. Halpern, New York, NY; and the Lawrence and Sandra Post Family. Dr. Elinav is the Incumbent of the Rina Gudinski Career Development Chair.

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